The Hazard Evaluation System and Information Service: A Physician's Resource in Toxicology and Occupational Medicine

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Hazard evaluation is an emerging science. The Hazard Evaluation System and Information Service (HESIS), part of California's program in preventive occupational health, is a resource for clinicians who wish to stay abreast of the relationship between toxicology and occupational health. For example, advances in assays for cancer or reproductive effects in test animals enable us to identify with greater confidence significant cancer or reproductive hazards among the increasing variety of workplace exposures. Occupational experiences with dibromochloropropane (DBCP), Kepone, bis(chloromethyl) ether, benzidine and vinyl chloride demonstrate the shortcomings of relying on human data. The latency period of cancer, limited sensitivity of epidemiologic studies and severity of effects require us to use animal test data to evaluate the potential cancer and reproductive risks of workplace substances. HESIS gives appropriate weight to experimental data in hazard evaluations of chemicals such as ethylene oxide, ethylene dibromide, polychlorinated biphenyls and the glycol ethers. A similar approach is apparent in the California Department of Health Services' recently released Carcinogen Identification Policy.

In 1977 male workers engaged in formulating commercial batches of several pesticides, including the nematocide dibromochloropropane (DBCP), at a chemical plant in Lathrop, California, realized that for several years none of them had fathered a child. Their fears of apparent infertility were confirmed when, with the cooperation and assistance of their union, the company and health professionals, semen analyses were conducted and the group was found to have an abnormally high prevalence of oligospermia (low sperm count) and azoospermia (absence of sperm).[1] The frequency and severity of these effects correlated well with the duration of the men's exposure to DBCP. Pronounced effects on spermatogenesis occurred at exposure levels as low as 0.4 ppm (eight-hour time-weighted average), doses that produced no other clinical signs of toxicity.[2]

Shortly thereafter, results from the National Cancer Institute Bioassay program were released showing that DBCP caused cancer in test animals at doses very close to those that workers at Lathrop might have received.[3] In addition to being a potent carcinogen, DBCP was also shown to be genotoxic in several short-term tests for mutagenicity using bacteria[4-6] or mammalian cells.[7,8]

The DBCP incident was the first documented example of workplace-induced reproductive failure in men. The rapidly differentiating reproductive tissue in male test animals seems to be particularly sensitive to certain chemicals (see Ethylene Dibromide later in this paper) as is the differentiating fetal tissue in pregnant women (see Glycol Ethers). Public concern was heightened by the discovery that studies were published 18 years earlier showing that DBCP caused testicular

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ABBREVIATIONS USED IN TEXT

DBCP = dibromochloropropane
HESIS = Hazard Evaluation System and Information Service
TIRS = Telephone Inquiry Response System

changes in test animals at dose levels close to those that produced similar adverse spermatogenic effects in the men.[9] Had greater significance been attached to these results in test animals, the reproductive failure in workers at Lathrop might have been avoided.

What can be done to help prevent similar episodes from occurring in the future? Two lessons may be learned. First, the release of information at the right time (for example, animal toxicity data on DBCP to plant officials and workers at Lathrop) could be an effective part of a program of preventative occupational medicine. Second, greater weight may need to be given to results from studies in test animals as predictors of effects in humans.

Shortly after the DBCP episode, the California legislature moved to strengthen the state's academic resources in occupational health and medicine by establishing several Occupational Health Centers on campuses of the University of California. Right-to-know legislation in California was enacted to enable employees and employers to receive information on the hazards of workplace substances and to permit employees (or their physicians) to have access to personal medical records. Finally, the legislature created the Hazard Evaluation System and Information Service (HESIS) within the State's Department of Health Services.*

Hazard Evaluation System and Information Service

HESIS practices preventive occupational medicine by providing information to workers and employers on the health effects of toxic substances used in workplaces and by assisting alert and concerned clinicians in identifying possible occupational determinants of disease. The HESIS scientific staff of occupational health physicians and PhD toxicologists attempts to bridge the gap between the published scientific and medical literature and the workplace community (employers, employees and health professionals) by a systematic review of current issues of 57 journals in toxicology, epidemiology, occupational medicine and related fields. These resources are present in the HESIS library. To provide the most up-to-date information possible on questions of toxicology and occupational health, the HESIS computer provides access to bibliographies of the world's published medical and toxicologic literature, US-sponsored research in progress and numerous medical, toxicologic and occupational health data bases.

HESIS provides information to the occupational health community in several ways. A Telephone Inquiry Response System (TIRS) is available to answer questions from employees, employers or health professionals about clinical symptoms or about toxic substances encountered in California's workplaces. HESIS staff, including scientists, health educators and a librarian, responded to over 1,000 such inquiries in 1981. Such calls may alert the medical community to new health hazards or may trigger follow-up investigations or remedial consultations.

TIRS serves as a listening post for the health problems of California's workplaces. With TIRS and a continual review of the scientific and medical literature and of data from various health registries (such as data on tumors and birth defects), HESIS has begun to create a reasonably comprehensive occupational health surveillance system for California. The cooperation of physicians is needed to improve and extend this system.

From such surveillance, HESIS on occasion conducts an in-depth investigation of a targeted substance, group of substances, health effect or occupation, and releases a written review of the scientific and medical evidence that documents the potential for hazard.[10-22] Following this evaluation, HESIS may inform the workplace community of any new or unappreciated health hazard by issuing a *Hazard Alert*,[23-25] *Information Bulletin*[26] or *Fact Sheet for Physicians*,[27-33] depending upon the apparent severity of the problem. As a consequence of such a hazard evaluation, HESIS may also recommend to Cal-OSHA that the work practices or permissible exposure level (PEL) for a substance be changed (examples are ethylene oxide [EtO],[23] glycol ethers[24] and ethylene dibromide [EDB].[25])

Cancer and Reproductive Hazards in the Industrial Chemical World

Over the past 40 years the production of synthetic organic chemicals has increased enormously (greater than 300-fold),[34] and workers are exposed to a much greater variety of chemicals than ever before. Few of these approximately 50,000 substances have been tested for their ability to cause such severe and life-threatening effects as cancer, mutation, birth defects or sperm damage. For those that have been studied, it has not been clear how animal test data, which provide most of the evidence, should best be used.

The long latency period of some human cancer (as long as 20 to 40 years)[35] raises the possibility that past and present workplace exposures will cause increases in cancer among workers in the future. Although the cancer rate of the general population at present appears to be relatively stable, lung cancer has increased significantly over the last 80 years.[36] The major portion of this increase is attributed to increased cigarette smoking,[37,38] but the contributions of occupational factors are less clear.[37,39] What *is* clear is that significant increases in cancer have occurred in certain workplaces during this same period—such as exposures to bis(chloromethyl) ether, asbestos, 2-naphthylamine and benzidine—without causing visible changes in the cancer incidence in the general population, and that unacceptably high cancer risks were experienced by indi-

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vidual workers from their exposure to carcinogenic agents.

Most of the known human carcinogens to which the public may be exposed have been identified by the high cancer rates observed among workers in specific industries: of the 36 agents for which there is strong or conclusive epidemiologic evidence of carcinogenic effect in humans, 26 were identified by occupational exposures; the remainder are mainly agents used in cancer chemotherapy (see Table 1).[40]

Although less time may be required to see the effects in workers from exposures to mutagenic or reproductive toxins, very little is known about the prevalence of these effects in workplace situations.[41] Effects on spermatogenesis have been studied for occupational exposures to only eight chemicals; clear or suggestive evidence is present for four chemicals other than DBCP[1,42-44] (lead,[45] carbon disulfide,[46,47] carbaryl[48,49] and dinitrotoluene/toluenediamine[50]); and no effects were seen with three others: polybrominated biphenyl (PBB),[51] p-*tertiary* butylbenzoic acid[52] and epichlorohydrin.[42] Adverse reproductive effects in male and female workers have been associated with workplace exposures to several substances.[53] In some cases, spontaneous abortions may arise from damage to sperm cells (see Table 2).

Cancer and reproductive disabilities are serious health hazards. They compel us to regulate workers' exposures to toxic substances and to use animal data where possible to prevent such outcomes from occurring in humans.

Assessment of Reproductive Hazards: The Value of Animal Data

The DBCP incident raises an important question: How can test results from studies of substances in ex-

TABLE 1.—*Chemicals, Groups of Chemicals and Industrial Processes That Are Carcinogenic or Probably Carcinogenic to Humans*

Carcinogenic

4-Aminobiphenyl
Arsenic and certain arsenic compounds
Asbestos
Manufacture of auramine
Benzene
Benzidine
N,N-bis(2-chloroethyl)-2-naphthylamine (chlornaphazine)*
Bis(chloromethyl)ether and technical grade chloromethyl methyl ether
Chromium and certain chromium compounds
Diethylstilbestrol*
Underground haematite mining
Manufacture of isopropyl alcohol by the strong acid process
Melphalan*
Mustard gas
2-Naphthylamine
Nickel refining
Soots, tars and mineral oils
Vinyl chloride

Probably Carcinogenic

Acrylonitrile
Aflatoxin*
Amitrole (aminotriazole)
Auramine
Beryllium and certain beryllium compounds
Cadmium and certain cadmium compounds
Carbon tetrachloride
Chlorambucil*
Cyclophosphamide*
Dimethylcarbamoyl chloride
Dimethylsulphate
Ethylene oxide
Iron dextran*
Nickel and certain nickel compounds
Oxymetholone*
Phenacetin*
Polychlorinated biphenyls
Tris(1-aziridinyl)phosphine sulphide (thiotepa)

*Evidence for effects in humans was obtained from nonoccupational exposures. Adapted from IARC, 1979.[40]

TABLE 2.—*Adverse Reproductive Effects Reportedly Associated With Occupational Exposures**

Chemical	*Reported Effects*
To Women	
Laboratory solvents[54-56]	(Chromosome aberrations); (birth defects)
Lead and/or other smelter exposures[57-60]	Spontaneous abortions; reduced birth weights; (congenital abnormalities)
Mercury (metal)[61]	(Abnormal ovarian function)
Anesthetic gases[62-70]	Spontaneous abortions; reduced birth weights; congenital malformations
Phthalate esters[71]	(Anovulation); (increased spontaneous abortions)
Formaldehyde[72]	Menstrual disorders; (increased spontaneous abortions); reduced birth weights
Carbon disulfide[73,74]	Menstrual disorders; increased spontaneous abortions; (reduced fertility)
Organochlorine pesticides[75-77]	(Abnormal ovarian function); (increased toxemia of pregnancy); (impaired lactation)
Benzene, toluene xylene[78]	Prolonged menstrual bleeding
Pesticides (various)[79-83]	Chromosome aberrations
To Men	
Dibromochloropropane (DBCP)[1,2,43,84,85]	Infertility, azoospermia, oligospermia
Lead and/or other smelter exposures[45,57,86-88]	Spontaneous abortions; premature births; [chromosomal abnormalities]; sperm abnormalities
Vinyl chloride[89-95]	[Chromosomal abnormalities]
Anesthetic gases[65,66,68]	Increased spontaneous abortions; congenital abnormalities
Kepone[96]	Loss of libido; reduced sperm counts
Carbon disulfide[47]	Decreased libido; impotence; increased sperm abnormalities
Ethylene dibromide[97]	(Decreased fertility)

Evidence is weaker for reported effects in ( ).
Events reported in nonreproductive tissues in [ ].

*Adapted from Council on Environmental Quality.[53]

TABLE 3.—*Comparison of Reported Teratogenic Effects in Humans and Experimental Animals for Seven Agents**

Agent	*Reported Sites in Humans*	*Reported Sites in Animals*
Anesthetic gases	Hemangiomas, hernias, skin, heart	Skeletal defects only: rat, mouse
Smelter emissions (lead and/or arsenic)	Multiple malformations	Multiple malformations: rat, mouse, hamster (lead and arsenic)
Polychlorinated biphenyls	Skin discoloration; enlarged fontanelles	Skin discoloration and lesions: rhesus monkey; enlarged fontanelles and syndactyly: pig, dog
Alcohol	Facial, central nervous system	Facial, dermal, neural, extremities: rat, mouse
Vinyl chloride	(Neural tube)	Various, including encephalocele: rat
Diphenylhydantoin	Cleft lip, cleft palate, other craniofacial, mental deficiency	Cleft lip, cleft palate, syndactyly, other skeletal defects: mouse; minor kidney anomalies: rhesus monkey
Methylmercury	Central nervous system	Central nervous system, skeletal: rat, mouse, hamster, cat

Evidence is weaker for reported effects in ( ).

*Adapted from Council on Environmental Quality.[53]

TABLE 4.—*Comparison of Lowest Effective Doses of Eight Teratogens in Humans and Animals**

Chemical	*Species*	*Ratio of Animal Dose: Human Dose*
Thalidomide[102,103]	Rabbit	5.0-2.5
Polychlorinated biphenyls[104,105]	Rhesus monkey	1.8
	Dog	14.3
Alcohol[106,107]	Rat	3.8-7.6
Aminopterin[108,109]	Rat	2.0
Methotrexate[110,111]	Rat	4.8
Methylmercury[112-114]	Cat, rat	50.0
Diethylstilbestrol (DES)[115,116]	Rhesus monkey	10.0-2.5
Diphenylhydantoin[117,118]	Mouse	25.0

*Adapted from Council on Environmental Quality.[53]

perimental animals best be evaluated and communicated so as to protect worker health? The interspecies comparisons that can be made between humans and animals for reproductive endpoints (such as spermotoxicity and teratogenicity) are interesting but are based on very limited data. Comparisons that have been made for semen parameters (counts, motility or morphology) between at least two species (including man) show a reasonably similar response for 24 chemicals.[98] Epidemiologic and laboratory studies that assay for semen quality (counts, morphology, or motility) in humans or animals are relatively easy to conduct and quite sensitive. If appropriate human study populations can be identified, a more meaningful comparison between the spermotoxic effects of chemicals in animals and humans may be made in the near future.

Teratogenicity

For teratogenic or embryotoxic endpoints, several thousand substances have been tested in experimental animals, and several hundred have been found to give a positive result.[99] Only a handful have been studied in humans, and fewer of these produce effects.[100] The infrequency of teratogenic events limits the sensitivity of epidemiologic studies, and makes it unlikely that the number of identified human teratogens will increase substantially in the near future.[101] Thus, our knowledge of the predictive value of animal teratogenicity data will likely remain limited. Nevertheless, for the several agents that have been examined, comparisons of their teratogenic *effects* and *potencies* reveals that the human and animal responses are not as dissimilar as might have been expected (see Tables 3 and 4). Thus, for reproductive toxins in general, there may be more of an overlap than we had imagined between agents that affect humans and those that produce effects in test animals.

Cancer Prevention in the Workplace

A first step in limiting cancer risks to individuals and the working population is to reduce the causes of major varieties of cancer—lung, colon-rectal and breast —and control exposures to specific cancer-causing substances. The major *identified* causes of lung cancer include tobacco smoke and asbestos,[38,119] and diet is believed to play an important role in breast and colon-rectal cancer.[120] In theory, cancer may be prevented by modifying the diet, controlling the use of tobacco and reducing exposures to cancer-causing substances such as asbestos. As a practical matter, involuntary environmental or occupational exposures may be easier to control than has been the voluntary use of tobacco or improper diet.

While attention has been focused on assessing the relative proportion of present and future cancer incidences that are caused by *either* "lifestyle" or occupational and environmental factors[37,39] (with varying estimates that need to be resolved by future studies[39]), an uncertainty of perhaps greater public health consequence may be overlooked. The effect of simultaneous exposures of workers to *both* factors, as is likely to occur in the workplace and in everyday life, is more relevant to an appropriate assessment of human risk. In two well-documented human studies of cancer risks from exposures to agents singly or in combination (cigarette smoking and exposures to asbestos or radiation), the cancer risks from the combined exposures are the *product,* not the sum, of the risks from separate exposures. Thus, prolonged cigarette smoking is associated with a tenfold increase in the risk for bronchial carcinoma (lung cancer) while prolonged heavy occupational exposure to asbestos is associated with a fivefold increase in risk. However, combined exposures

(such as cigarette smokers exposed to asbestos) are associated with a 50-fold, and not 15-fold, increase in risk over that experienced by nonsmokers with no asbestos exposure.[119] There are data to suggest that a similar synergism exists between exposures to tobacco smoke and radiation.

Such synergistic interactions may be more common than is currently appreciated, but at present we cannot predict whether the effects of other interactions will be additive, multiplicative or inhibitory. Thus, from a policy as well as a scientific standpoint, the dichotomy between "lifestyle" and environmental and occupational factors may be more artificial than helpful. A simpler view is that cancer has a multiplicity of interacting causes, including "lifestyle" and environmental and occupational exposures, and that these will only infrequently be disentangled.

Oncogenes and Cancer

Oncogenes[149-156] have been isolated from tumors of several human tissues (bladder, breast and lung), the sites of the major types of cancer in humans. When introduced into normal cells, these genes transform the cells into a cancerous state. Genes with similar transforming abilities have been isolated from tumors of these same tissues from test animals. Whereas distinctly different cancer genes exist for bladder, breast and lung, it is significant that the oncogenes from human and test animals are virtually identical for a specific tissue. In addition, some of these genes are virtually identical to the cancer-causing genes of the common tumor viruses that produce cancers in animals.

Even more remarkable is the finding that such genes are present in normal cells where they may participate in the maintenance of daily cellular functions. Damage to these genes (or to other controlling genes) by carcinogens or tumor virus infection may stimulate their activity and lead to cancer.

While much remains to be described of the mechanism of action of cancer genes, the recent discoveries suggest a unifying theory of cancer-causation that is gratifyingly simple. Normal cells contain certain genes necessary for normal cellular function. Modification (mutation, rearrangement and the like) of these genes (or of other genes that normally restrain their activity) by carcinogens or tumor virus infection causes them to function abnormally. This genetic misbehavior converts the cell to cancerous growth.

Methods for Identifying Carcinogens

A carcinogen is generally understood to be a substance or agent that increases the frequency (age-specific incidence) of cancer in humans or in other species.[40,121-129] The identification of chemical substances that pose cancer risks to humans is complex and requires integration of information from several scientific disciplines. Evidence that a substance may be a carcinogen comes from four sources: epidemiologic studies in human populations; bioassays in experimental animals; short-term tests for mutagenicity and cell transformation, and similarities in chemical structure to known carcinogens. Procedures for evaluating data from the first three of these methods are reviewed briefly; it should be noted that they provide evidence of different strengths.

Epidemiologic Studies

Epidemiologic studies offer the overwhelming advantage of providing direct evidence for carcinogenic effects in *humans*. They are well suited to identify major causes of cancer in defined populations (cigarettes, asbestos, initial pregnancy late in life and so forth)[130] but are less suited to determining whether a *specific* chemical poses a cancer risk to humans. Even so, epidemiology has identified several important chemical carcinogens (such as benzene, arsenic) before animal tests were done.[40] At present, the International Agency for Research on Cancer states that there is sufficient evidence for the carcinogenicity in humans of 18 chemicals, groups of chemicals and industrial processes, and there is probable evidence of varying strengths for 18 others[40] (see Table 1).

In addition, negative results from well-conducted epidemiologic studies are useful in placing an upper limit of risk for a chemical exposure. They complement the more uncertain quantitative risk estimates made from data from animal cancer tests.

Epidemiologic methods are extremely useful tools. In general, however, they have low sensitivity. For example, when a cohort study population is relatively small (less than 1,000), the study may fail to identify an agent that increases the risk of a specific type of cancer by a factor of less than five to ten. Even large-scale studies may require an increase of more than 50 percent in cancer incidence before an effect is statistically significant. For this reason, negative results in studies of smaller size seldom provide strong evidence that an agent is not carcinogenic. To detect a carcinogenic effect, it may be necessary to have either a very large study population or a smaller-sized population that is exposed for several years to large doses of a potent carcinogen. In addition, such studies are often difficult to conduct, both because appropriate study groups and reliable information about past exposures are limited and because biases and confounding factors are difficult to eliminate. A recent review[131] reports that epidemiologic data do not exist (and are unlikely to be developed in the future) for the vast majority of industrial chemicals that cause cancer in experimental test animals and to which workers are exposed.

In addition, because of the 20- to 30-year latency period of many types of cancer in humans, epidemiologic studies are not suited to warn and protect people from the cancer risks from exposures to new carcinogens. If an early-stage carcinogen has been identified by an epidemiologic study as a cause of human cancer and the exposures are reduced or eliminated, the cancer risk among those previously exposed may remain appreciable for the ensuing 20 to 30 years. Limiting exposure to late-stage carcinogens or promoters can reduce the cancer risk more rapidly—for example, ces-

sation of cigarette smoking appears to modify the risk for lung cancer within five years.[132,133]

Thus, because of the insensitivity of epidemiologic studies, the long latency period of cancer and the difficulty in obtaining an appropriate study population, we are forced to rely heavily on other means of identifying agents which have the potential to produce cancer in humans.

Assessment of Cancer Hazards: The Value of Animal Data

Fortunately, results from animal cancer bioassays appear to be reasonable qualitative predictors of carcinogenic effects in humans, and the laboratory animal bioassay is widely used to indicate the carcinogenic potential of a chemical. Bioassay methods have been standardized in recent years and, except for minor details, there is now general acceptance of test procedures.[125,134-140] Most substances that are carcinogenic in one species of test animal are carcinogenic in a second when adequately tested;[141-148] most substances that are known to be carcinogenic in humans, for which adequate animal data exist, are carcinogenic to animals.[40,146-148] For several recognized human carcinogens—4-aminobiphenyl, bis(chloromethyl) ether, diethylstilbestrol, melphalan, mustard gas and vinyl chloride—the first evidence of carcinogenicity was found in test animals. Only afterwards were cancer effects looked for, and found, in humans.[148] From a scientific standpoint, it seems reasonable to consider substances for which there is evidence of toxic effects in test animals as likely to produce similar effects in humans. Thus, the International Agency for Research on Cancer concludes, "In the absence of adequate data in humans it is reasonable, for practical purposes, to regard chemicals for which there is *sufficient evidence* of carcinogenicity (i.e., a causal association) in animals *as if they presented a carcinogenic risk for humans*"[40] [emphasis added].

Indeed, recent discoveries in the molecular biology of cancer would make it surprising if carcinogenesis in rodents is greatly different from that in humans. Cancer-causing genes ("oncogenes") and cell transformation maintenance factors have been isolated from rodent tissues and are virtually identical to those found in the corresponding human tissues.[149-156] These findings indicate that carcinogenesis in humans and test animals may be remarkably similar, and they strongly support the belief that test animals are reasonable and appropriate models for understanding the carcinogenic process in humans.

Sufficient evidence presently exists for the carcinogenicity in animals of about 200 chemicals. The International Agency for Research on Cancer considers there is "sufficient evidence" for carcinogenicity for 142 of the 422 chemicals it has assessed in its review process.[40] The National Cancer Institute has concluded that there is "sufficient evidence" of carcinogenicity for 98 of the 190 chemicals evaluated in its bioassay program,[144] some of which are the same as those reviewed by the International Agency for Research on Cancer. As stated earlier, sufficient evidence exists for 18 chemicals that they are carcinogenic in humans.[40]

For most of the 200-odd animal carcinogens for which there is "sufficient evidence," it is unlikely that we will ever know with certainty whether they cause cancer in humans because of the difficulty in obtaining appropriate populations suitable for epidemiologic studies. Since it is unlikely we will ever confirm or deny the apparent carcinogenic potential of these 200 chemicals, it appears prudent in the interim to control exposures to them as if they had demonstrated effects in humans.

Short-term Tests for Mutagenicity, DNA Damage and Cell Transformation

Short-term tests[157-159] generally evaluate the ability of a substance to produce mutations, chromosomal alterations or DNA damage in a test organism, or to induce transformation of cultured mammalian cells. Systems that are used in short-term tests include microorganisms (such as bacteria, yeast and molds), cultured mammalian cells and whole animals. These tests are comparatively inexpensive ($5,000 to $10,000 per battery of short-term tests versus $500,000 for an animal bioassay) and can be completed in a relatively short time. A number of these tests can be done, therefore, with limited resources. They offer the potential for providing useful information on the two most intransigent problems in carcinogenic risk assessment—species differences between rodents and humans, and estimating risks at very low doses. Some short-term tests can be performed with human cells or tissues; and some effects, such as DNA damage, can be measured at very low doses.

Use of short-term tests to predict carcinogenicity is justified on both theoretical and empirical grounds. Many of these tests detect biological activities (mutagenicity and cell transformation) that are believed to be stages of carcinogenesis. Most known animal and human carcinogens have been shown to be mutagenic when tested in a suitable battery of short-term tests, while most noncarcinogens have not.[160-169] Because of this, a battery of tests can be a useful predictor of carcinogenicity. Such a strong correlation may exist because most of the chemical carcinogens tested thus far act by mechanisms that involve DNA damage, though this has not been rigorously proved. The particular relevance of tests that measure cell transformation is based on the observation that transformed cells, when implanted into a receptive animal host (such as a "nude" mouse) will form malignant tumors.

There is a high probability that a chemical that is *positive* in an appropriate battery of short-term tests will prove to be a carcinogen when adequately tested in animal cancer tests. Short-term tests can be used, therefore, to augment evidence for carcinogenicity from animal cancer bioassays that, for some reason, are not by themselves definitive. Short-term tests can also indicate the *potential* for carcinogenic hazard of chemicals not yet tested in animals. At present, short-term tests are not sufficiently standardized and validated to

provide *definitive* information about carcinogenicity or noncarcinogenicity in the absence of other evidence.

Risk Assessment and Hazard Evaluation

Quantitative estimates of cancer risks in humans based on extrapolation from animal data are difficult to interpret but are routinely made. What information needs to be developed to permit meaningful estimates of cancer risks from exposures to combinations of chemicals such as occurs in occupational settings? What is a reasonable occupational health policy in the interim? Some principles are emerging. Although differences may exist between species in host responsiveness (differences in pharmacokinetics and DNA-repair efficiencies, for instance), the carcinogenic potencies of chemicals in different species of test animals (rats and mice) are generally similar.[170] Moreover, the responsiveness of test animals is reasonably similar to that of humans for those chemicals (21) that have been examined.[170,171] Clearly, the inadequacy of human exposure data limits the accuracy of such comparisons. Such *inter*species differences as exist between rodents and humans must be viewed in relation to the presumed large variation among individuals (such as genetic heterogeneity and host-response differences) in the human population.

Information is needed to improve the accuracy of quantitative estimates of cancer risk from exposures to combinations of agents. In the interim, carcinogenic risks to humans exposed to single or combinations of chemicals must be estimated by extrapolation from available bioassay data using suitable (such as a multistage model) methods, while acknowledging that such methods will *underestimate* the true risks if synergisms occur. Compared with the population of test animals, the population of workers is genetically diverse and is simultaneously exposed to a large number of chemicals. Suitable corrections for these differences also should be made in any appropriate risk calculations.

Summaries of hazard evaluations carried out by HESIS for several substances are given below. The evidence for carcinogenicity or reproductive toxicity of these chemicals is based largely on results from studies in test animals.

Ethylene Oxide

Ethylene oxide[10] is a gas that is familiar to most health professionals as a widely used sterilant for heat-sensitive hospital supplies and equipment.[10] Recent studies have indicated that it is carcinogenic by inhalation in male and female rats (leukemia) at dose levels below the current permissible exposure level (50 ppm).[10,172] It is also mutagenic in 13 test systems,[10] including mammalian somatic cells (micronucleus test)[173] and germ cells (dominant lethal[174,175] and heritable translocation tests).[175] In addition, increased frequencies of sister-chromatid exchanges are found in the chromosomes of workers exposed to ethylene oxide[176] at doses less than one-tenth of the current permissible exposure level.[177] Similar chromosomal effects are produced in test animals (monkeys and rabbits).[178] Adverse reproductive effects (reductions in litter size of exposed female rats at 100 ppm,[179] and sperm count in monkeys at 50 ppm)[10] are evident in test animals at dose levels close to the permissible exposure level.

There is inadequate epidemiologic evidence to assess the carcinogenic or adverse reproductive effects of ethylene oxide in humans.[180-183] However, because of the extensive evidence for genotoxicity in test animals, HESIS issued a Hazard Alert[23] on this chemical and recommended that the permissible exposure level be reduced and that extensive programs in equipment maintenance, environmental monitoring, training and education, and medical surveillance be initiated in hospitals using this substance.

Hospitals are not normally considered to be workplaces where exposures to toxic substances occur. However, the example of ethylene oxide indicates that members of the medical community, like workers in other occupational settings, need to be aware of the potential health hazards of toxic substances present in their work environment.

Formaldehyde

Like ethylene oxide, formaldehyde is a gas for which there is extensive evidence of genotoxicity and carcinogenicity. Formaldehyde is carcinogenic in two strains of rats and in one strain of mice (nasal cavity squamous cell carcinoma)[184,185] (Kern WD, Paukov KL, Donofri DJ, et al: Inhalation carcinogenicity of chronic formaldehyde exposure in rats and mice, unpublished data, 1982) at dose levels (6 to 15 ppm) near the current permissible exposure level (2 ppm). It causes DNA damage, mutation or transformation in four test species (bacteria,[186,187] yeast,[188] *Drosophila melanogaster*[189] and mammalian cells[190]) as well as chromosome aberrations in four species.[191] Epidemiologic evidence available at present has not shown a carcinogenic effect of formaldehyde in humans.[192-194] (Fayerweather WE, Pell S, Bender JR: Case-control study of cancer deaths in Du Pont workers with potential exposure to formaldehyde, unpublished report from E. I. Du Pont de Nemours & Co., May, 1982.) However, many of these studies had limited power to detect a significant increase in cancer incidence, and little or no information on exposure levels of formaldehyde was available.

Because the genetic toxicology of formaldehyde is very similar to that of ethylene oxide, it seems reasonable to adopt similarly safe work practices for formaldehyde and extend the health consciousness of the medical community into other work environments. A significant difference between the two chemicals is that formaldehyde is a potent nasal irritant and, thus, has good warning properties whereas ethylene oxide is a nearly odorless, nonirritating substance and, consequently, has poor warning properties. (In fact, a major health hazard from formaldehyde exposure may be respiratory sensitization.)

Ethylene Dibromide

Ethylene dibromide (EDB)[19,20] has major uses as a lead scavenger in leaded gasoline and as a soil fumigant

in agriculture. With the Med-fly crisis in the summer of 1981, a major increase in use of the chemical was proposed to fumigate citrus fruits, cherries and plums as a means of limiting the spread of Med-fly larvae.

HESIS staff had previously targeted ethylene dibromide as a priority chemical because its genetic toxicology was strikingly similar to that of the closely related brominated compound, DBCP.[19,20] Both chemicals are potent carcinogens, mutagens and spermotoxins with effects occurring in test animals at dose levels close to the permitted exposure levels in workers[20] (see Table 5). They are among the most potent carcinogens of the widely used industrial chemicals that have been tested in animal bioassays[192] (see Table 6). Ethylene dibromide and DBCP are carcinogenic in rats and mice of both sexes, producing the same malignant tumors at the tissue of first contact (oral route: stomach squamous cell carcinomas;[3,196] inhalation: respiratory tract carcinomas[197,198]). For ethylene dibromide, these effects occurred between 1 and 10 mg per kg of body weight per day, uncomfortably close to the dose that workers could receive (7 mg per kg of body weight per day)[192] at the then current permissible exposure level (20 ppm).

As with DBCP, the chemical is also a potent mutagen in several short-term tests for mutagenicity, including the Ames *Salmonella* test,[199] and *Drosophila*.[200] Also, like DBCP, it is a proved animal testicular toxin, causing effects on sperm or male-transmitted reproductive outcomes in three species where it is roughly as potent as DBCP (although in different species and by different routes of exposure, see Table 5).[20] To date, there have been no published reports of infertility or induced semen defects in humans associated with exposure to ethylene dibromide.[207,208]

Because of the extensive evidence that ethylene dibromide is a potent carcinogen and testicular toxin in test animals, HESIS issued a Hazard Alert[25] and recommended that the permissible exposure level be reduced (it is now 130 ppb in California). As was the case with ethylene oxide[23] and with the glycol ethers[24] (see below), the Hazard Alert was distributed to all companies, unions and workers in California who had potential exposures to the chemical. It is to be hoped that the lessons of DBCP have been learned so that human disease from exposure to these chemicals need never be observed.

TABLE 5.—*Effects of Ethylene Dibromide (EDB) and 1,2-Dibromo-3-chlorpropane (DBCP)*

	Route	*Dose*	*Effect*
Potent sperm toxins			
DBCP:			
Rats[9]	Inhalation	1.2	↓Atrophy
Rabbits[201]	Inhalation	0.5	↓Count
EDB:			
Cattle[202-204]	Oral	2	↓All
Rams[205]	Subcutaneous	8-14	↓Morphology
Rats[206]	Injection	10	↓Litter size

Species	*Oral*	*Inhalation*
Tumors produced from oral and inhalation exposures to DBCP and EDB		
Mice ♂,♀	Stomach squamous cell carcinomas	Nasal cavity adenocarcinomas
Rats ♂,♀	Stomach squamous cell carcinomas	Respiratory tract carcinomas

Polychlorinated Biphenyls

Polychlorinated biphenyls (PCB's)[14] have received considerable public notoriety as ubiquitous contaminants of our environment. Because they are complex mixtures that are chemically inert, heat stable and nonflammable, they have a variety of uses as dielectric fluids in transformers, hydraulic lubrication fluids, plasticizers and as components in inks, paints and adhesives.[14] They are carcinogenic in male mice (liver carcinomas)[210] and in two strains of female rats.[209,211] They cause transformation of mammalian cells in culture (DH Norback, PhD, and R Weltman, PhD, University of Wisconsin Medical School, oral communication, 1980). However, polychlorinated biphenyls are only 1/100 as potent as carcinogenic agents in test animals as ethylene oxide, formaldehyde, ethylene dibromide and DBCP, and the evidence for their genotoxicity is less extensive (see Table 6).

The highly chlorinated isomers of polychlorinated

TABLE 6.—*Chronic Toxicity of Widely Used Industrial Chemicals*

Chemical	*1981 US Production (in millions of lbs.)*	*Use*	*Carcinogenicity*			*Mutagenicity (Number of Different Short-Term Test Systems)*	*Permissible Exposure Level (PEL) (ppb)*
			Response		*Relative Dose to Produce Response**		
			Rats	*Mice*			
1,2-Dibromo-3-chloropropane (DBCP)	Not produced	Fumigant	4+	4+	1	+(5)	2
Ethylene dibromide (EDB)	250	Gasoline additive; fumigant	4+	4+	1	+(3)	125
Ethylene oxide (EtO)	5,000	Intermediate; sterilant	3+	+	10	+(13)	2,000
Formaldehyde (HCHO)	6,000	Intermediate	2+	+	10	+(7)	2,000
Polychlorinated biphenyls (PCB's)	Not produced	Dielectric		3+	100	Cell transformation (1)	
Trichloroethylene (TCE)	130 (1977)	Solvent	+	4+	1,000	+(4)	25,000
Glycol ethers (GE)	1,225	Solvent			...	−(7)	

*Relative dose (mg/kg/day) required to produce significant tumors (DBCP = 1; approximate values).

biphenyls are not readily metabolized in mammalian species, including humans, and tend to bioaccumulate in adipose tissues.[14] Thus, *although the carcinogenic risk is less well established for these chemicals than for the other chemicals already discussed, it is amplified by the long residence time of these agents in the body*. Because of these factors, HESIS recommended[14] that exposure to polychlorinated biphenyls be kept to a minimum.

Glycol Ethers

Glycol ethers[11] are a group of widely used industrial solvents found in cleaning and thinning agents and in coatings such as epoxies, wood stains, varnishes, paint and ink. They also serve as surfactants in various extraction processes and as fixatives in perfumes, cosmetics and soaps.[11]

Recent studies have shown that the glycol ethers and derivatives produce adverse reproductive effects in laboratory animals,[11] although they are negative in a variety of short-term tests for mutagenicity.[212,213] They induced birth defects in the offspring of exposed females and caused retarded sperm development and testicular growth in exposed males in three species (mice,[214,215] rats[215,216] and rabbits[215,216]). These effects occurred by a variety of dose routes (dermal, ingestion and inhalation) and at dose levels that were only slightly higher than the permissible exposure level for these compounds. The congenital defects observed were severe, including neural tube defects in mice (spina bifida and exencephaly)[214] and cardiac abnormalities in rabbits.[216,217] Rabbits were particularly sensitive to the testicular effects of ethylene glycol monomethyl ether, and degenerative changes in the testicular germinal epithelium were evident in one study from exposure to 30 ppm for 90 days (permissible exposure level: 25 ppm)[218] (Miller RR, Calhoun LL, Yano BL: Ethylene glycol monomethyl ether: 13-week vapor inhalation study with male rabbits, unpublished report from Dow Chemical, USA, submitted by the Chemical Manufacturers Association, 1982). Moreover, cardiovascular defects were observed in the offspring of rabbits that received ethylene glycol monoethyl ether.

There is inadequate evidence to assess the reproductive effects of glycol ethers in humans. Women exposed to a variety of solvents, including a glycol ether, reported a variety of gynecological disorders, and their newborn children had a higher incidence of birth defects (including congenital heart defects) than did newborns from a control group.[219] The significance of the birth abnormalities is tempered by the workers' exposures to other solvents.

Because of the severity of the reproductive effects in test animals, HESIS issued a Hazard Alert[24] and recommended that the permissible exposure level for the glycol ethers be lowered and that work practices be changed (use of impermeable gloves, protective clothing and good ventilation) to reduce skin and inhalation exposures. It is noteworthy that male and female reproductive tissues are affected by such nonreactive, nongenotoxic substances as the glycol ethers. Other solvents that share the special hydrophilic and lipophilic solvating ability of these substances could produce similar effects and should be tested.

Conclusions

Research on cancer and reproductive effects is continuing, and as our understanding increases, programs for prevention and control of these diseases will likely change. Prevention, however, can proceed without precise answers, and we must make occupational health decisions based upon the best available evidence. Cancer risks to the working population and to the individual person can be reduced by a comprehensive program to modify the major identified determinants of cancer and to control exposures to specific carcinogenic substances.[220] Similar programs should be possible with reproductive agents. Modification of work practices cannot be constrained to require absolute certainty when the consequences of inaction could result in serious effects on the health and welfare of the working population.

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